IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Declaration under 37 C.F.R. 1.132 Mail Stop After Final Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket	STAN-190
	First Named Inventor	D. Zeng
	Application Number	09/844,544
	Filing Date	April 27, 2001
	Group Art Unit	1644
	Examiner Name	M. Dibrino
	Title: Methods for Inhibition of Polyclonal B Cell and Immunoglobulin Class Switching to Pathogenic Autoantibodies by Blocking CD1-Mediated Interactions	

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

I, Dr. Samuel Strober, do hereby declare as follows:

I am a co-inventor of the above captioned patent application. I have read and understood the Office Action of October 21, 2003, and the references cited therein, particularly with respect to the rejection of claims 1, 2, 6, 7, 8, 10, 12 and 13 as being unpatentable over Amano *et al.* (1998), in view of Kotzin *et al.* (1996), Zeng *et al.* (1998); Blumberg *et al.* (1995) and Hughes (1998). I am also senior author of the cited Amano *et al.*, and Zeng *et al.* papers.

The present claims are directed to a method of treatment for pathogenic polyclonal B cell activation or class switching in a patient, by the administration of antibodies or fragments thereof that bind to CD1 and interfere with T cell recognition of CD1. Key to the invention is our demonstration *in vivo* that blocking CD1 by administration of antibodies significantly reduced the peak levels of serum IgG and IgG anti-dsDNA autoantibodies, and delayed disease progression. Importantly, these results were obtained with a spontaneous disease model, in contrast to the prior art model, which required a highly artificial transfer of genetically modified cells. These results were unexpected in view of the cited art.

The Examiner has cited our work, published as Amano *et al.* (1998). It is stated in the Office Action that: "Amano et al. teach that th interaction between anti-CD1 T cells and B cells

expressing surface CD1 leads to a mutual activation of both cell types that results in hypergammaglobulinemia and systemic autoimmunity *In vivo* via cross-linking of CD1 to secrete IgM and IgG. Amano et al further teach that transgenic CD1 + T cells (Vb9/Va4.4 T cell clones) induce lupus (SLE, and autoimmune disease) when transferred into nude mice which do not spontaneously develop lupus and that spontaneous secretion of IgM and IgG by splenic B cells from lupus prone mice is mediated by CD1 hi subset of B cells."

The Office Action concludes that T cell proliferation of the said CD1-restricted T cell clone in response to CD1-transfected B cells could be blocked by the use of the anti-CD1d mAb 3C11.

I note that as a matter of correctness, the experiments described above were published in the Zeng *et al.* paper, not by Amano *et al.*, although Amano *et al.* briefly refer to the work, without disclosing the underlying data.

It is critical to the understanding of the unexpected results in the present patent application, that one understand the cells involved in recognition of CD1. CD1 is not an antigen for conventional T cells, which are restricted to the major histocompatibility antigens by their receptor. However, there is another class of cells, termed NKT cells, ~~termed NK T cells~~, which are neither typical T cells nor typical NK cells, but which bear an α/β antigen receptor, ands some of the markers typical of NK cells. These cells have a restricted antigen receptor repertoire, predominantly made up of an invariant rearrangement of the Vα14 and Jα281 gene segments, associated with Vβ7 or Vβ8 receptor. This receptor seems to be restricted to interacting with glycolipid antigens presented by the cell-surface molecule, CD1. NKT cells are also apparently limited in their cytokine repertoire.

The work described by Amano *et al.* related to recognition of the CD1 molecule in the absence of β_2-microglobulin, a protein component required for MHC class I molecules to properly function in antigen presentation.

Amano *et al.* demonstrate that a T cell clone with an invariant Vβ9/Vα4.4 rearrangement proliferated in response to a B cell line transfected with CD1 encoding sequences. The T cell clone also proliferated in response to splenic LPS-activated wild type cells, which response was inhibited by the monoclonal antibody 3C11.

What these experiments show is that certain NKT cell clones, which are isolated and grown in culture, and which have a specific invariant rearrangement of the T cell receptor, are able to recognize CD1 as a stimulating antigen (for example, see 1714, under the heading T cell

recognition is not associated with β_2m). However, **these experiments do not show that B cells are stimulated by the T cell.**

It is a hallmark of lupus that the disease is associat d with polyclonal B cell activation and class switching. The proliferation of T cells is interesting, but is not informative of a disease that is caused by B cells.

The work in my laboratory that is referred to in the above paragraph from the Office Action was published by Zeng *et al.* In this work, the T cell receptor noted by Amano *et al.* (Vβ9/Vα4.4), which was associated with proliferation in response to CD1, was cloned, and inserted as a transgene into an animal.

The transgene is then expressed in a majority of T cells in the animal. But because these coding sequences are artificially introduced, expression is not restricted to the NKT cells population, but rather is found on conventional T cells, which have different properties that NKT cells. The transgenic cells used in this work are (a) artificially found at a very high concentration; (b) artificially expressing a receptor on a different class of cells and (c) artificially transferred into a host animal.

Because of the many artificial features of this model system, one could not draw any conclusions, certainly not conclusions with reasonable certainty, about the role of CD1 in lupus. In particular, the subset of cells that express the transgene is an important point.

Amano *et al.* report a double negative cell line that is **$CD4^-CD8^-$**, which expresses the Vβ9/Vα4.4 receptor, and which proliferates in response to CD1. (see Amano *et al.*, page 1714, paragraph under the heading "T cell recognition of CD1 is not associated with β_2m"). On the other hand, the same T cell receptor, when expressed as a transgene, was associated with single positive cells (**$CD4^+CD8^-$** or **$CD4^-CD8^+$**) in one transgenic mouse; and with double negative cells (**$CD4^-CD8^-$**) in another mouse. (see Zeng *et al.* page 526, last paragraph).

The key importance of this is that the injection of the double negative cells, which correspond to the cells that originally expressed the transgene, were **protective of disease**, while the single positive cells, which do not correspond to the original cell type, **caused a disease** phenotype.

One of skill in the art would have reason to believe that the cells tested by Amano et al., which expressed Vβ9/Vα4.4 in a double negative cell, would prevent disease. The only pathological cells were those that artificially expressed the Vβ9/Vα4.4 transgene in a single positive cell, and even then, only after transfer to a secondary animal host, while the primary transgenic animal does not develop disease.

Therefore, the data presented by Zeng *et al.* (1998) demonstrate that animals transgenic for a T cell receptor that recognizes CD1 do not develop disease; and that certain populations of the T cells can be transferred to cause disease, while other populations of T cells, which are more representative of native populations, suppress disease. From these findings, one of skill in the art could not conclude with any degree of certainty that CD1 would have a causative effect in spontaneous lupus. Although the art suggested a possible connection between spontaneous lupus and CD1, there was substantial uncertainty that CD1 had a causative role, or was merely associated with the disease in these systems. Without the findings provided in the present application, one of skill in the art could not have a reasonable certainty of success practicing the claimed methods.

I hereby declare that all statements made herein of my own knowledge are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Date: 12/18/03

By _____

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